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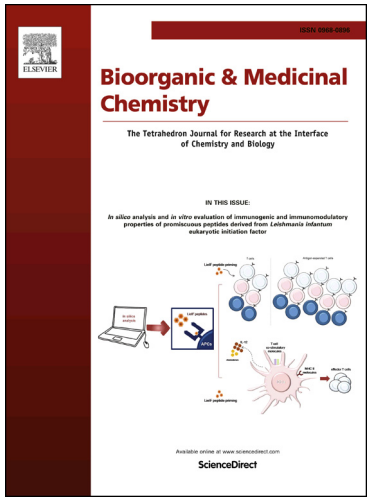

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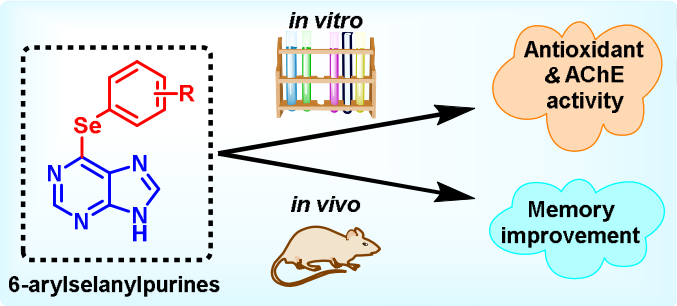

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ABSTRACT

We describe here a simple method for the synthesis of 6-arylselanylpurines with antioxidant and anticholinesterase activities, and memory improvement effect. This class of compounds was synthesized in good yields by a reaction of 6-chloropurine with diaryl diselenides using $NaBH_4$ as reducing agent and PEG-400 as solvent. Furthermore, the synthesized compounds were evaluated for their *in vitro* antioxidant and acetylcholinesterase (AChE) inhibitor activities. The best AChE inhibitor was assessed on the *in vivo* memory improvement. Our results demonstrated that the 6-((4-chlorophenyl)selanyl)-9*H*-purine and 6-(*p*-tolylselanyl)-9*H*-purine presented *in vitro* antioxidant effect. In addition, 6-((4-fluorophenyl)selanyl)-9*H*-purine inhibited the AChE activity and improved memory, being a promising therapeutic agent for the treatment of Alzheimer's disease.

1. Introduction

Nucleoside analogues show significant roles in numerous biological processes.[1] There are five nitrogenous bases that form the nucleosides, and two of them are purines (adenine and guanine). Up till now, there are over 30 nucleoside analogues approved for use as antiviral or cytotoxic agents and almost 50% of these molecules containing structurally transformations on the pyrimidine/purine ring.[2] The structure of purines consist in a pyrimidine fused to an imidazole and they are the most widely distributed nitrogen heterocycles in nature.[3] Therefore, synthetic approaches have been developed for the synthesis of structurally diverse purine derivatives, which possess several biological activities such as antitumor, antitubercular, fungicidal and antioxidant effects.[4] The 6-position at the purine ring is a principal modification place for many of these applications.[5]

In the other hand, selenium is a trace element being considered an essential dietary nutrient for all mammals. This element presents several physiological functions as structural component of diverse antioxidant enzymes, playing important role in metabolic pathways, including hormonal metabolism and immune function.[6]

Additionally, the interest in the organoselenium pharmacology and chemistry has increased in the last two decades due to a variety of selenium compounds that possess biological activities. Organoselenium derivatives are considered attractive synthetic targets, owing to their special structural motifs and unique reactivity.[7] Indeed, a number of important pharmacological properties have been attributed to organoselenium compounds, such as antioxidant,[8] anti-inflammatory,[9] neuroprotective,[10] anxiolytic-like,[11] antihyperglycemic,[12] among others.

In this sense, selenium-containing purines are an interesting class of compounds since they combine the well-known applicability of the purine skeleton with that of the selenium moieties. Thus, the synthesis of selenium-containing purines[13] has great significance and as example, alkylselanylpurines have shown activity as an inhibitor of the growth of mouse leukemia L1210[14] and could be used in the treatment of neural measles virus infection.[15]

In view of the above mentioned, and according our interest in the synthesis and biological evaluation of nitrogen-functionalized organoselenium compounds,[16] we report here our results on the

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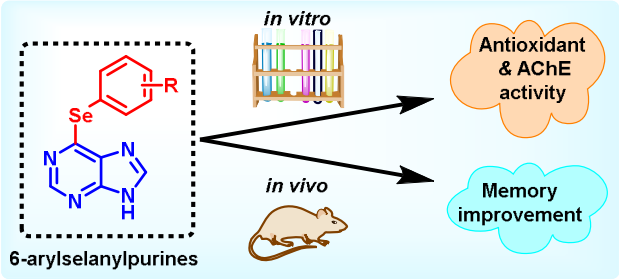
synthesis of 6-arylselanylpurines by reactions of 6-chloropurine with diaryl diselenides and $NaBH_4$ using PEG-400 as solvent. In addition, the synthesized compounds were screened for their *in vitro* antioxidant action and inhibitory effect on the cerebral acetylcholinesterase (AChE) activity. Considering the obtained *in vitro* results, we investigated the activity of compound with better inhibitory effect on the AChE activity on the three stages of memory (acquisition, consolidation and retrieval) in mice.



Scheme 1. General scheme of the present work.

2. Materials and Methods

2.1. Chemistry

The reactions were monitored by TLC carried out on Merck silica gel (60 F254) by using UV light as visualizing agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 300 MHz or 400 MHz on Bruker DPX 300 or DPX 400 spectrometers, respectively. Spectra were recorded in $CDCl_3$ and DMSO-*d6* solutions. Chemical shifts are reported in ppm, referenced to the signal of tetramethylsilane (TMS) as the external reference or DMSO signals. Coupling constants (*J*) are reported in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet) and m (multiplet). Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 75 MHz or 100 MHz on Bruker DPX 300 or DPX 400 spectrometer, respectively. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ or DMSO-*d6*. Low-resolution mass spectra were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker Micro TOF-QII spectrometer 10416.

2.1.1. *General procedure for the synthesis of 6-arylselanylpurines **3a-h**:*

To a round-bottomed flask containing a solution of diorganyl diselenide **1a-h** (0.25 mmol) in PEG-400 (1.0 mL) under N_2 atmosphere, was added $NaBH_4$ (1.0 mmol). The resulting solution was stirred for 1 hour at 60 °C, when its color changes from yellow to colorless. After this, the 6-chloropurine **2a** (0.5 mmol) was added and the mixture was stirred at 60 °C for additional 1 hour. Then, the desired product was precipitated when the pH was adjusted to 6 using 6 N HCl. The product was collected, washed with H_2O and then purified by recrystallization. The new compounds were fully characterized and the spectral data are provided in the Support Information.

2.1.2. *General procedure for the synthesis of N-Heterocycle-SePh **3i-m**:*

To a round-bottomed flask containing a solution of diphenyl diselenide **1a** (0.25 mmol) in PEG-400 (1.0 mL) under N_2 atmosphere, was added $NaBH_4$ (1.0 mmol). The resulting solution was stirred for 1 hour at 60 °C, when its color changes from yellow to colorless. After this, the appropriated chlorine substituted nitrogen heterocycle **2b-f** (0.5 mmol) was added and the mixture was stirred at 60 °C for additional 1 hour. Then, the reaction mixture was received in water (10 mL), extracted with ethyl acetate (3 x 5 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate/hexanes as the eluent. The new compounds were fully characterized and the spectral data are provided in the Support Information.

2.2. Biological assays

2.2.1 Animals

Male adult Swiss mice (25-35 g) from our own breeding colony were used. The animals were kept on a separate animal room, in a 12 h light/dark cycle, at a room temperature of 22 ± 2ºC, with free access to food and water. Animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, Federal University of Pelotas, Brazil (CEEA 1974-2016).

2.2.2. 2,2'-Diphenyl-1-picrylhydrazyl (DPPH) radicals scavenging activity

In the DPPH assay, the reduction of DPPH radical by antioxidants could be through the donation of hydrogen atom to a free radical to remove the extra electron (which is responsible for the activity of free radicals).[17] A DPPH stable radical assay was performed in accordance with Choi et al..[18] Briefly, DPPH was added to a medium containing compounds (**3a**-**3g**) at different concentrations (1-200 µM). Compounds were solubilized in dimethyl sulfoxide (DMSO) before the use. Compound **3h** was not used in the assay because it not solubilized efficiently in DMSO. The medium was incubated for 30 min at room temperature. For each assay, 3 independent experiments were carried out in different days. The decrease in absorbance was measured at 517 nm, which depicted the scavenging activity of purine derivatives (**3a**-**3g**) against DPPH. The values were expressed in % of blank: DPPH radicals scavenging activity = (absorbance of sample x 100) / absorbance of blank.

2.2.3. 2,2'-Azino bis-3-ethylbenzothiazoline-6 sulfonic acid (ABTS) radicals scavenging activity

ABTS is a protonated radical and it is used for evaluating the scavenger activity of proton radicals.[17] The ABTS radical assay was performed in accordance with Re et al..[19] In short, ABTS was added to a medium containing purine derivatives (**3a**-**3g**) at different concentrations (1-200 µM). Compounds were solubilized in DMSO before the use. Compound **3h** was not used in the assay because it not solubilized efficiently in DMSO. The medium was incubated for 30 min at room temperature. For each assay, 3 independent experiments were carried out in different days. The decrease in absorbance was measured at 734 nm, which depicted the scavenging activity of purine derivatives (**3a**-**3g**) against ABTS. The values were expressed in % of blank: ABTS radicals scavenging activity = (absorbance of sample x 100) / absorbance of blank.

2.2.4. AChE activity assay

Animals were killed by inhalation of isoflurane, and cerebral cortex were quickly removed, placed on ice and homogenized 1:10 (w/v) in Medium I (0.32 M sucrose, 5.0 mM HEPES, 0.1 mM ethylenediaminetetraacetic acid disodium salt) buffer. The homogenate was centrifuged at 2400*x*g at 4ºC for 15 min to yield the low-speed supernatant (S_1) fraction that was used in the assays. For each assay, 3 independent experiments were carried out in different days, using different animals. The AChE activity

of cerebral cortex was performed according to the method of Ellman et al.[20] with some modifications, using acetylthiocholine iodide as a substrate. An aliquot of 50 µl of the S_1 (protein of 2.8 mg/ml) was pre-incubated for 2 min at 25ºC in the presence of compounds **3a-3g**, at different concentrations (1-200 µM) in a medium containing potassium phosphate buffer 100 mM, pH 7.5. Compounds were solubilized in DMSO before the use. Compound **3h** was not used in the assay because it not solubilized efficiently in DMSO. Enzymatic reaction was initiated by adding 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) to a final concentration of 0.5 mM and acetylthiocholine to a final concentration of 0.8 mM. The rate of hydrolysis of acetylthiocholine iodide was measured at 412 nm through the release of the thiol compound which when reacted with DTNB, produces the color-forming compound thionitrobenzene (TNB). The activity of AChE was expressed as µmol acetylthiocholine/h/mg protein. The protein concentration was measured by the method of Bradford[21] using bovine albumin serum (1 mg/ml) as a standard.

2.2.5. Behavioral tasks - In vivo

Considering the *in vitro* results of purine derivatives on the cerebral AChE activity, compound with better inhibitory effect was used on the behavioral tasks. Mice were allowed to acclimatize to the holding room for 2 h before the behavioral procedure. All manipulations were conducted in the light phase.

2.2.5.1. Step-down inhibitory avoidance:

Non-spatial long-term memory was investigated using a step-down inhibitory avoidance task according to the method of Sakaguchi et al.,[22] with modifications in the intensity of electric shock and in the exposure time. Each mouse was placed on the platform, and the latency to step-down (four paws on the grid) was automatically recorded in training and test sessions. In the training session, upon stepping down, the mouse received a 0.5 mA scrambled foot shock for 2 s. Test sessions were performed 24 h later, with the same procedure except that no shock was administered after stepping down; an upper cut-off time of 300 s was set. Six to eight animals were used per group. Compound **3e**, which inhibited AChE activity *in vitro*, was given 30 min before training (acquisition), immediately post-training (consolidation), or 30 min before test (retrieval), at the dose of 10 mg/kg of body weight (intragastrically (i.g.)). Control animals received vehicle (canola oil 10 ml/kg of body weight, i.g.).

2.2.5.2. Open-field test:

Spontaneous locomotor and exploratory activities were measured in the open-field test.[23] The open-field was made of plywood and surrounded by walls 30 cm in height. The floor of the open-field, 45 cm in length and 45 cm in width, was divided by masking tape markers into 9 squares (3 rows of 3). Each animal was placed individually at the center of the apparatus and observed for 4 min to record the locomotor (expressed by number of segments crossed with the four paws) and exploratory (expressed by the number of time rearing on the hind limbs) activities. Six to eight animals were used per group. The locomotor and exploratory activities were evaluated after the test session of the step-down inhibitory avoidance task.

2.2.6. Statistical analysis

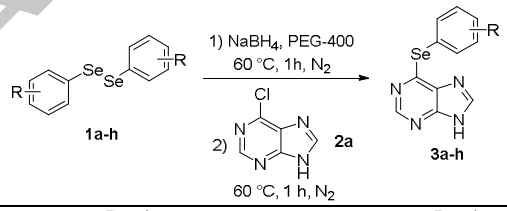
For *in vitro* assays, statistical analysis was performed using a one-way ANOVA followed by the Newman–Keuls test when appropriated and the results were expressed as mean ± standard derivation (S.D.). Maximal inhibition (I_{max} - maximum percentage that an inhibitor reduced a response) was calculated at the most effective concentration used. For *in vivo* experiments, the data were analyzed using a non-paired t-test and the results were expressed as mean ± standard error medium (S.E.M.). Values of $p < 0.05$ were considered statistically significant.

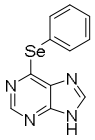
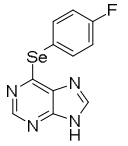
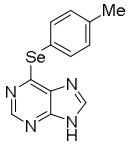
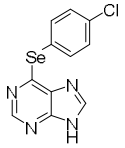
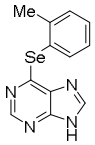
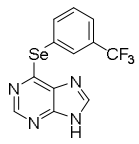
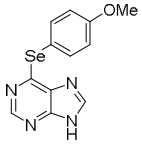
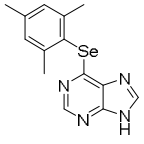
3. Results and Discussion

3.1. Chemistry

In the last years our research group has continuously explored the potential of $NaBH_4$/PEG-400 as reaction system to promote different synthetic transformations.[7e,24] Thus, based in our previous works and considering that there are no reports of the use of this system to promote the insertion of organochalcogen moieties into purine nucleus, we decided to study the efficiency of this reaction medium to promote the functionalization of purine derivatives by employing different diaryl diselenides as source of organochalcogen nucleophilic species. First, in a mixture of diphenyl diselenide **1a** (0.25 mmol) in PEG-400 (1.0 mL) under N_2 atmosphere, we added $NaBH_4$ (1.0 mmol) and the reaction was stirred for 1 hour at 60 °C. After this time, the 6-chloropurine **2a** (0.5 mmol) was added and the mixture was stirred at 60 °C for additional 1 hour. Through this protocol the desired 6-phenylselanyl-purine **3a** was successfully obtained in 96% yield, after 1h (Table 1, entry 1). Importantly, the use of only 0.5 equivalent of PhSeSePh on this experiment suggests that both "PhSe" moieties are being consumed for the final product formation, which represents an advantage of this method regarding to atom economy.

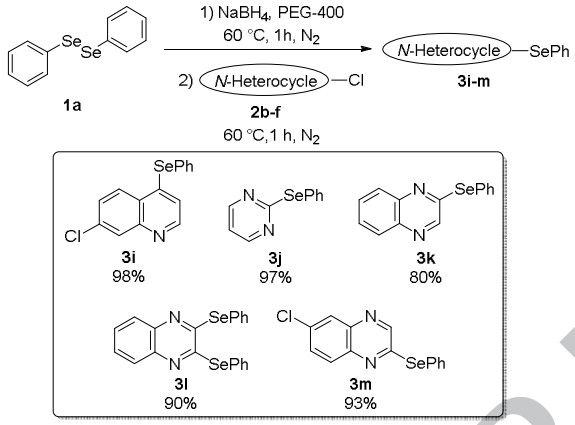
Table 1. Variability in the synthesis of 6-arylselanylpurines.[a]



Entry	Product (Yield)[b]	Entry	Product (Yield)[b]
1	 **3a** (96%)[c]	5	 **3e** (55%)
2	 **3b** (74%)	6	 **3f** (86%)
3	 **3c** (65%)	7	 **3g** (95%)
4	 **3d** (87%)	8	 **3h** (55%)

[a] Reactions were performed using diorganyl diselenide **1a-h** (0.25 mmol), $NaBH_4$ (1.0 mmol) in PEG-400 (1 mL) at 60 °C under N_2 atmosphere for 1 h. After this, 6-chloropurine **2a** (0.5 mmol) was added and the mixture was stirred at 60 °C for additional 1 hour. [b] Yields are given for isolated products. [c] One reaction was performed in a 5 mmol scale and the desired product **3a** was obtained in 90% yield.

Encouraged by this promising result we have focused on verify the versatility of this synthetic methodology using differently substituted diaryl diselenides. These tests showed that this synthetic approach is not sensitive to electronic effects from the substituents in the aromatic rings of the diselenides. Diaryl diselenides bearing neutral, donating and electron-withdrawing groups afforded the expected 6-arylselanyl-purines **3a,d-g** in good to excellent yields (Table 1, entries 1,4-7). On the other hand, the target heterocycles **3b**, **3c** and **3h** were obtained in 74, 65 and 55% yields, respectively. These results suggest that the reaction behavior has being affected by steric hindrance from the methyl groups bonded to the aromatic rings of the diselenides (Table 1, compare entries 2,3 and 8).



Scheme 2. Variability in the synthesis of *N*-Heterocycle-SePh.

In order to extend the scope and confirm the versatility of the synthetic method different chlorine substituted nitrogen heterocycles were submitted to the same reaction condition in the presence of diphenyl diselenide **1a**. When the 2-chloropyrimidine and 2-chloroquinoxaline were employed as substrates the corresponding 2-phenylselanyl-pyrimidine **3j** and 2-phenylselanyl-quinoxaline **3k** were isolated in 97 and 80% yields (Scheme 2). By employing the 2,3-dichloroquinoxaline as starting reagent under the optimized reaction conditions the 2,3-bis(phenylselanyl)quinoxaline **3l** was obtained in excellent yield by the replacement of the two chlorine atoms by both "PhSe" moieties from the diphenyl diselenide.

Interestingly, when 4,7-dichloroquinoline and 2,6-dichloroquinoxaline were submitted to the same reaction conditions the desired heterocycles **3i** e **3m** were isolated in excellent yields and these transformations carried out with high regioselectivity since in all cases only one chlorine atom was replaced by the organochalcogen group (see Scheme 2).

These results increase the synthetic importance of this methodology once the preservation of a chlorine atom in the final product structure allows further functionalization of the heterocycle units by using several synthetic tools.

3.2. Biological assays

3.2.1. In vitro antioxidant activity of purine derivatives: DPPH and ABTS radicals scavenging activities

Synthetic radicals DPPH and ABTS have been used for the determination of scavenger mechanism of antioxidants molecules.[25] In the DPPH assay, antioxidant molecules donate hydrogen to free radical, removing the extra electron, which is responsible for the damage caused by free radical. In the present study, it was verified that compound **3f** demonstrated DPPH radical scavenging activity at concentrations equal to 200 µM (Table 2). The I_{max} of compound **3f** was 32%. Compounds **3a**, **3b**, **3c**, **3d**, **3e** and **3g**, at all concentrations used, did not show DPPH radical scavenging activity (Table 2).

Like radical DPPH, ABTS radical is also used to check the scavenger activity of antioxidants.[26] In the ABTS assay, protonated ABTS radical is used to evaluate the scavenger activity of proton radicals, which are an important attribute of antioxidant molecules.[17] Our results showed that compounds **3b** and **3f** presented a significant ABTS radical scavenging activity at concentrations equal to or greater than 100 µM, while compound **3a** demonstrated scavenger activity at concentrations equal to 200 µM (Table 3). The I_{max} values of compounds **3a**, **3b** and **3f** were 13.5, 38.5 and 27.4%, respectively. Compounds **3c**, **3d**, **3e** and **3g**, at all concentrations used, did not present ABTS radical scavenging activity (Table 3).

3.2.1. In vitro AChE activity assay

AChE is an enzyme with a key role in cholinergic neurotransmission by hydrolyzing the acetylcholine to acetate and choline in the synaptic cleft.[27] AChE inhibitors are strategies of treatment to Alzheimer's disease.[28] Nowadays, the Food and Drug Administration (FDA) approved four AChE inhibitors for the treatment of Alzheimer's disease (tacrine, donepezil, galanthamine and rivastigmine). However, these drugs have low bioavailability and undesirable side effects. Thus, this study reported inhibitory effect of purine derivatives (**3a**-**3g**) on AChE activity in cerebral cortex of mice.

Table 2. Effect of purine derivatives **3a-3g** in the DPPH radical scavenging activity.

	Purine derivatives						
	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
Blank	100.0 ± 10.0	100.0 ± 10.0	100.0 ± 10.0	100.0 ± 10.0	100.0 ± 10.0	100.0 ± 10.0	100.0 ± 10.0
1 µM	99.4 ± 0.9	100.7 ± 0.5	100.2 ± 0.4	99.8 ± 0.6	99.4 ± 1.0	100.0 ± 1.0	99.7 ± 0.4
10 µM	99.4 ± 0.2	99.7 ± 0.8	100.0 ± 0.7	99.7 ± 0.9	99.4 ± 0.6	98.8 ± 1.5	99.4 ± 0.9
100 µM	95.1 ± 1.1	96.3 ± 0.7	99.3 ± 0.5	98.5 ± 0.4	98.6 ± 1.0	85.9 ± 2.6	99.4 ± 0.6
200 µM	90.1 ± 2.1	93.0 ± 1.8	98.7 ± 0.4	97.5 ± 0.5	98.0 ± 1.4	68.0 ± 3.3*	99.0 ± 1.8

Data are reported as mean ± S.D. of 3 independent experiments. DPPH radical scavenging activity was expressed as % of blank. * $p < 0.05$ as compared with the blank group (one-way ANOVA/Newman-Keuls).

Table 3. Effect of purine derivatives **3a**-**3g** in the ABTS radical scavenging activity.

	Purine derivatives						
	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
Blank	100.0 ± 10.0	100.0 ± 10.0	100.0 ± 10.0	100.0 ± 10.0	100.0 ± 10.0	100.0 ± 10.0	100.0 ± 10.0
1 µM	99.9 ± 0.7	100.1 ± 1.9	99.3 ± 0.7	100.9 ± 1.0	99.7 ± 2.1	99.5 ± 1.2	99.4 ± 1.1
10 µM	98.8 ± 0.6	98.0 ± 1.3	96.9 ± 2.0	98.1 ± 1.6	100.9 ± 1.1	98.4 ± 1.1	98.9 ± 0.4
100 µM	93.2 ± 0.8	81.7 ± 4.7*	97.7 ± 1.3	97.1 ± 0.3	99.7 ± 1.2	86.5 ± 1.8*	97.9 ± 1.3
200 µM	86.5 ± 0.6*	61.5 ± 7.4*	94.8 ± 1.4	93.5 ± 0.9	96.9 ± 0.4	72.6 ± 1.2*	97.6 ± 0.7

Data are reported as mean ± S.D. of 3 independent experiments. ABTS radical scavenging activity was expressed as % of blank. * $p < 0.05$ as compared with the blank group (one-way ANOVA/Newman-Keuls).

Table 4. Effect of purine derivatives **3a**-**3g** on AChE activity in cerebral cortex of mice.

	Purine derivatives						
	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
Control	9.6 ± 0.5	9.6 ± 0.5	9.6 ± 0.5	9.6 ± 0.5	9.6 ± 0.5	9.6 ± 0.5	9.6 ± 0.5
1 µM	7.8 ± 1.5	8.7 ± 2.4	7.9 ± 1.2	10.4 ± 1.6	6.6 ± 0.6*	7.2 ± 1.7	7.9 ± 0.9
10 µM	7.6 ± 1.1	9.3 ± 2.9	7.6 ± 1.0	11.3 ± 2.4	6.5 ± 0.4*	7.3 ± 1.2	8.9 ± 1.7
100 µM	7.7 ± 1.0	8.9 ± 2.4	7.1 ± 1.5	11.0 ± 3.0	6.6 ± 1.7*	7.8 ± 1.6	8.2 ± 1.3
200 µM	7.6 ± 1.1	8.9 ± 1.9	6.3 ± 0.9*	8.8 ± 2.3	6.6 ± 1.3*	7.8 ± 1.4	8.2 ± 1.6

Data are reported as mean ± S.D. of 3 independent experiments. AChE activity was expressed as µmol acetylthiocholine/h/mg protein. * $p < 0.05$ as compared with the control group (one-way ANOVA/Newman-Keuls).

Table 4 shows the effect of purine derivatives (**3a**-**3g**) on AChE activity in cerebral cortex of mice. Compounds **3c** and **3e** significantly inhibited the cerebral cortex AChE activity at concentrations equal to or greater than 200 and 1 µM, respectively. The I_{max} values were 34.4% for compound **3c** and 31.2% for compound **3e**. Compound **3e** had an inhibitory effect on the AChE activity at concentrations less than **3c**. Purine derivatives **3a**, **3b 3d**, **3g** and **3f** had no effect in inhibiting AChE activity in cerebral cortex of mice.

3.2.1. ***Behavioral tasks – In vivo***

Progressive loss of memory is a major feature of Alzheimer's disease. Memory can be defined as the record of information representation acquired through experiences, and it is a process that has several stages.[29] Moreover, cholinergic system has a key function in the memory.[30] Thus, considering the *in vitro* results of purine derivatives on the AChE activity, compound **3e** was used to investigate its effect in improving memory in mice.

Figure 1 shows the effect of purine derivative **3e** on the step-down inhibitory avoidance task in mice. During the training session in the step-down inhibitory avoidance task, there was no difference in the step-through latency time among groups.

Compound **3e** administered 30 min before the training (acquisition) did not change the step-through latency time (Figure 1A). However, administration immediately after the training session (consolidation) (Figure 1B) and 30 min before the test session (retrieval) (Figure 1C) increased (around 52 and 44%, respectively) the step-through latency in comparison to the control group. Acquisition, consolidation and retrieval are stages of memory[29] and we verify that purine derivative **3e** caused a cognitive enhancement in the memory phases of consolidation and retrieval.

Administration of compound **3e** pre-training, immediately post-training and before test did not cause impairment in the locomotor activity (number of crossings) and exploratory behavior (number of rearing) of mice assessed by the open-field test (data not shown).

4. Conclusion

In summary, we describe a simple method for the synthesis of 6-arylselanylpurines with antioxidant and anticholinesterase activities, as well as in improving memory. This method involves the reaction of the commercial available 6-chloropurine with nucleophilic selenium species, generated in the system $(ArSe)_2/NaBH_4/PEG\text{-}400$. The reactions are suitable to a range of diorganyl diselenides and proceeded efficiently at 60 °C under N_2 atmosphere furnishing the products in moderated to excellent yields. Biological studies revealed the promising antioxidant effects of the synthesized arylselanyl purine derivatives. Moreover, it was evidenced the inhibitory effect on the cerebral AChE activity by a purine derivative (compound **3e**) containing fluorine in the chemical structure. Still, this purine derivative administrated in mice caused cognitive enhancement in the memory phase of consolidation and retrieval in the step-down

inhibitory avoidance task, being a promising therapeutic agent for the treatment of Alzheimer's disease.

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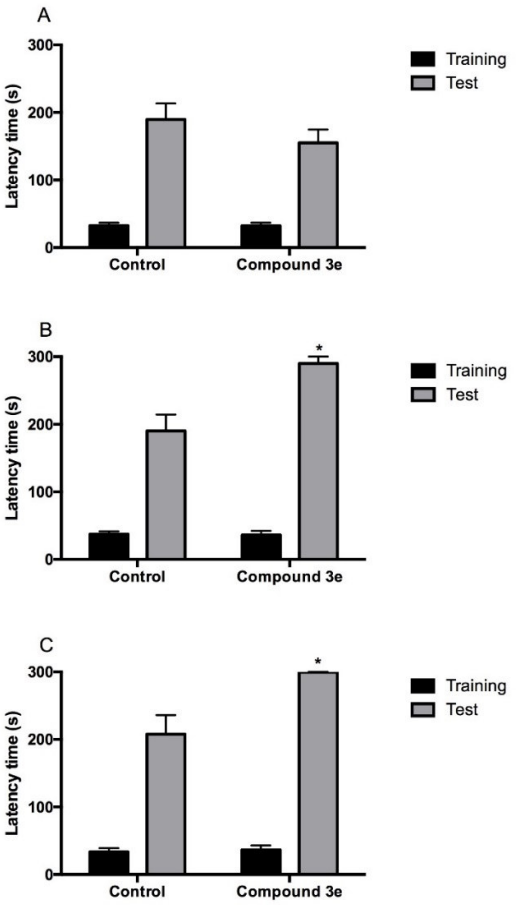

Figure 1. Effect of purine derivative **3e** on the step-down inhibitory avoidance task in mice. Compound at the dose of 10 mg/kg was administered, intragastrically, 30 min before training session (acquisition) (A), immediately post-training (consolidation) (B) and 30 min before test (retrieval) (C). Each column represents mean ± S.E.M. for 6 to 8 animals per group. Data were analyzed using a non-paired t-test. (*) $p < 0.05$ when compared to the control group.

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